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# TRANSMITTAL FORM

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		Application Number	09/881,326
		Filing Date	06/14/2001
		First Named Inventor	David Rozema
		Group Art Unit	1636
		Examiner Name	William Sandals
Total Number of Pages in This Submission	4	Attorney Docket Number	Mirus.013.04.02

## ENCLOSURES (check all that apply)

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<input checked="" type="checkbox"/> Amendment / Reply	<input type="checkbox"/> Licensing-related Papers	<input type="checkbox"/> Appeal Communication to Group (Appeal Notice, Brief, Reply Brief)
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<input type="checkbox"/> Affidavits/declaration(s)	<input type="checkbox"/> Petition to Convert to a Provisional Application	<input type="checkbox"/> Status Letter
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<input type="checkbox"/> Response to Missing Parts under 37 CFR 1.52 or 1.53	Attached is a signed copy of the originally faxed Supplement.	

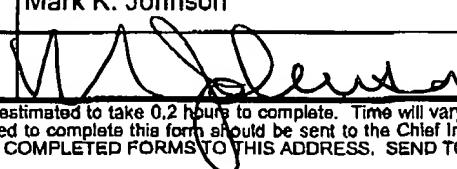
## SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm or Individual name	Mirus Corporation
Signature	
Date	01/20/2003

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Typed or printed name	Mark K. Johnson
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## IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

#11  
PP  
1-22-03  
(NB)

Application of: Jon A. Wolff, )  
James E. Hagstrom, Sean D. Monahan, )  
Paul M. Slattum, David B. Rozema and )  
Vladimir G. Budker )  
Serial No.: 09/881,326 )  
, Filed: 06/14/2001 )  
Group Art Unit: 1636 )  
Examiner: William Sandals

For: **Intravascular Delivery of Non-Viral Nucleic Acid**

SUPPLEMENTAL INFORMATION

Commissioner for Patents  
Washington, D.C. 20231

Dear Sir:

Applicants have attached information that they believe is pertinent to the examination of this case. In particular, the information has been copied from the file history of the U.S. Patent No. 5,698,531 issued to Nabel *et al.* which is the primary prior art cited in Applicants' case.

Applicants wish to supplement their argument that the '531 patent does not teach transfection of extravascular parenchymal cells. The information provided also supplements the telephone interview held on Thursday, January 16, 2003 between Applicants and the Examiner where Applicants call attention to an article reviewing the state of gene delivery published by Elizabeth Nabel (Circulation. 1995;91:541-548.). Elizabeth Nabel states on page 544, 1<sup>st</sup> column, last paragraph:

"Several observations concerning the delivery of recombinant genes and patterns of gene expression can be drawn from these studies. Infusion of vector into normal arteries with an intact endothelium results in transfection of intimal cells (primarily endothelial cells). [at this point, Ms. Nabel cites her own work among others published well after the filing date of the '531 patent.] Injury to the vessel and/or application of pressure to the vector infusate results in delivery of DNA transmurally and gene expression in the media".

This paragraph dictates the overall extent of transfection into blood vessels in 1995 as well as the '531 inventors' ability to 'teach' the art in years prior to 1995: 1) transfection

into intimal cells (1<sup>st</sup> layer of vasculature without injury; and 2) transfection into medial cells (2<sup>nd</sup> layer of vasculature) with injury.

As further evidence of the '531 inventors' lack of ability to teach Applicants' delivery methods, Applicants call the Examiner's attention to the file history of the '531 patent. In the amendment filed on November 22, 1993, page 3, the inventors limit their teachings to "site-specifically transforming cells." On page 5 site-specificity is limited to "using physical methods to place the DNA or RNA sequences at specific locations." On page 10 of the '531 amendment, the inventors provide data to show delivery to vessel cells and lack of delivery to extravascular cells by  $\beta$ -galactosidase activity: "In addition, no  $\beta$ -galactosidase activity was observed in random microscopic segments from the liver, lung, or kidney, except for cells with endogenous activity."

Importantly, on page 19 of the same amendment, the '531 inventors attempt to differentiate their process from a prior art process and thereby limit their '531 teachings to a physical method of delivery (injury to the endothelial wall): 'Firstly, Myers [prior art to Nabel *et al.*] differs from the present invention in that it uses the vector as a homing beacon to ensure that the DNA sequence reaches the appropriate cell. In contrast, the present invention uses physical methods to deliver recombinant genes to specific lesions *in vivo* and differs from Myers targetable injectable vector.' Applicants point out that in the '531 inventors' own language they state that they must deliver to "specific lesions" which are caused by their denuding processes and differs from an injectable vector.

In a further limitation to the '531 teachings, Paper 19, an Office Action to the '531 inventors, states on page 2: "Clearly a syringe, as would be used for injection purposes, would be materially distinct from the balloon catheter". In Paper 26, an examiner interview summary record attempts to convince Nabel *et al.* to "reduce issues of prior art" by limiting their claims to a balloon catheter, stating: "Examiner suggested bringing out balloon catheter concept in the method claims." Nabel *et al.* respond and finally limit their claims to a catheter.

By their own statements, the inventors of the '531 patent have limited their teachings to physical denuding of vessel walls followed by physical delivery to specific locations of a vessel wall. One would have to ignore logic to conclude that the '531 patent teaches non-local delivery of genetic material to extravascular parenchymal cells by injection as taught by Applicants.

Applicants request that the Examiner contact them regarding this correspondence after his consideration.

Respectfully submitted,

Mark K. Johnson Reg. No. 35,909

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